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Aggregation of the Amyloid-β Protein: Monte Carlo Optimization Study

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The free-energy approach has delivered promising results for protein folding and structure prediction in recent years. The native state is found as the global minimum of an all-atom free-energy forcefield. Now, we used this approach to simulate the aggregation of Aβ fragment 16-22. This aggregation is believed to be associated with the Alzheimer's disease. The model system contained 2 polypeptide chains. The obtained structures of the aggregates consisted of either parallel or anti-parallel β-sheets, the latter were preferable.

1 Introduction

The Alzheimer's disease is associated with misfolding of the amyloid protein. In the functional native form, this small protein, of 42 amino acids, has globular structure with two α-helices. However, under certain conditions, it can form aggregates of β-sheets that, on a larger scale, are arranged as long insoluble fibrils[3]. The resulting fibrils have toxic effects in the extracellular space of the brain of patients with the Alzheimer's disease. The amyloid protein in this form is known as Aβ peptide.

This protein has been extensively studied by both experimental and computational methods[8,7]. The experimental techniques such as solid-state NMR, X-diffraction and electron microscopy were used for characterizing the structure of aggregates[8]. Most of the computational studies were focused on short polypeptide fragments of this protein, such as $LYS_{16} - LEU - VAL - PHE - PHE - ALA - GLU_{22}$[4]. This fragment is believed to play a key role in the formation of the aggregates. In the present work, we study the systems of one and two chains of Aβ_{16-22} peptide[2].

2 Methods and Results

The free-energy approach has delivered promising results for protein folding and structure prediction in recent years. Following Anfisen's hypothesis[1] the native state is postulated to be the global minimum of a all-atom free-energy function. This minimum can be found by optimization methods[9] including the Monte Carlo procedure. This approach was successfully used to fold α-, β- and mixed proteins of moderate length[10,12,5].

This approach requires an accurate, transferable protein free-energy forcefield. In this study we used Protein Force Field (PFF02)[6,11]. In our model, all the atoms are explicitly represented (the apolar group CH_n is considered as a single atom). The bond angles and the bond lengths are fixed. The degrees of freedom considered are the backbone (ψ, ϕ) and the sidechain (χ_i) dihedral angles.

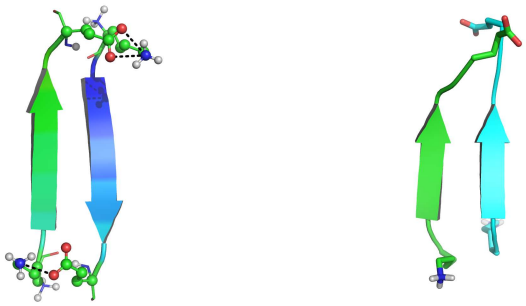

Figure 1. **Left:** The lowest energy structure is an anti-parallel β-sheet. The polar contacts between side-chain atoms N of LYS_{16} and O of GLU_{22} are shown explicitly. **Right:** The energy of the best parallel β-sheet structure is higher by 10 kcal/mol.

The energy function contains the following terms: (1) the standard Lennard-Jones potential, (2) the Coulomb energy of electrotatic interaction with group specific dielectric constants, (3) a term for the hydrogen bonding, (4) a SASA-based solvation term that implicitly takes into account the influence of the solvent. We used several optimization methods used to find the global minimum of the energy function: (1) basin hopping technique (BHT), (2) parallel tempering, and (3) evolutionary strategies[9].

Recently, our protein simulation package, POEM, has been modified to treat multiple polypeptide chains. In the present study, we simulated the systems of one and two chains of Aβ_{16-22} using a modified version of BHT[12]. In the simulations of a single chain, no specific unique structure was formed, in agreement with the earlier studies[4]. In contrast, the system of two chains formed an anti-parallel β-sheet in most of the cases. The lowest energy structure is shown in Fig. 1. The main reason for the antiparallel orientation has been much debated in the literature, the two options being the salt bridges[7] and the efficient sidechain packing[4].

Analysis of the simulations shows the overwhelming preference for the anti-parallel orientation. The free energy surface of the two-chain system is presented in Fig. 2. The lowest energy structures are the anti-parallel β-sheets. However, in the simulations the parallel orientation was also observed. The parallel β-structure with the lowest energy is shown in Fig. 1. The anti-parallel orientation is stabilized by the efficient sidechain packing as well as by the polar interactions between the sidechains of LYS_{16} and GLU_{22}.

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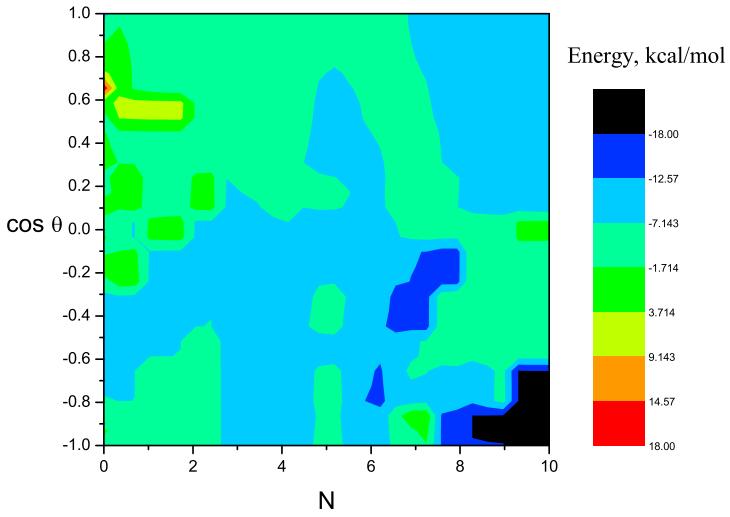

Figure 2. The free energy surface of the two-chain system. The co-ordinates are the number N of the residues in the β-conformation and the cosine of the angle θ between the two end-to-end vectors.

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